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Is Time of Renal Hypoperfusion an Important Variable in Determining Response to Renal Artery Revascularization?

The CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial found that stent implantation did not provide any benefit beyond optimal medical therapy in the occurrence of death or adverse cardiovascular or renal events in patients with moderately severe atherosclerotic renal artery stenosis (1). There was a modest, consistent difference in systolic blood pressure favoring the stent group, but this did not result in a decrease in adverse clinical outcomes. These findings are consistent with the ASTRAL (Angioplasty and Stenting for Renal Atherosclerotic Lesions) trial (2) and the STAR (Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery) trial (3).

Over the years, studies of renal artery intervention have been criticized for small sample size, the use of angioplasty alone rather than stenting, high treatment-crossover rate, and enrollment of patients with renal artery lesions that were not hemodynamically significant. CORAL is the largest study of renal artery intervention and anticipated all of these potential criticisms. Even though the threshold for enrollment in CORAL was lowered to include stenosis of $\geq$60%, a subgroup analysis limited to patients with stenosis $\geq$80% did not show any benefit to stent implantation.

Why have the clinical trials of stenting of atherosclerotic renal artery stenosis failed to show improved clinical outcomes? One variable that might play an important role in determining the benefit of revascularization is the time of renal hypoperfusion. In the 2-kidney-1-clip model, abrupt onset of decreased renal perfusion is associated with renin-angiotensin system activation, leading to sodium and water retention. Over time, the renin-angiotensin system returns to baseline levels and the intact normal kidney compensates to excrete sodium and water by pressure natriuresis (4). Transient activation of the renin-angiotensin system leads to elevated oxidative stress, sympathoadrenergic activation, and impaired vasoactive responses within both the kidney and the systemic microcirculation (5). Moreover, animal studies show that persistent ischemia leads to irreversible kidney damage and development of a chronic kidney disease phenotype (6). Similar renal damage is seen in humans; the majority of patients with renal artery stenosis have renal parenchymal changes including interstitial fibrosis, tubular atrophy, glomerulosclerosis, periglomerular fibrosis, and a variety of arteriolar abnormalities (7). Finally, there is evidence that short-term elevation in angiotensin II levels can accelerate the development of atherosclerosis and lead to changes in the arterial wall that persist even after angiotensin levels return to baseline (8,9). It is unclear to what extent, if any, that these adverse renal and vascular effects respond to revascularization.

Data from animal models suggest that renal parenchymal damage and aortic atherosclerotic changes begin soon after renal hypoperfusion. These effects worsen over time and many of the changes are irreversible. Further studies are needed to determine whether there is a "window of time" in humans during which revascularization is beneficial and whether it can be identified with biomarkers or renal imaging.

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http://dx.doi.org/10.1016/j.jcin.2013.12.001

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